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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	17

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Application No.	Applicant(s)
09/439,293	[redacted]
Examiner	Art Unit
Jane Zara	1635

Office Action Summary

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR [illegible]
- after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory [illegible]
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) [illegible]
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED [illegible]
- Any reply received by the Office later than three months after the mailing date of this communication, even if [illegible]
earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____

2a)☐ This action is **FINAL** 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-8,10-15,17-19,21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-8,10-15,17-19,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1☐ Certified copies of the priority documents have been received.

2☐ Certified copies of the priority documents have been received in Application No. _____

3☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

KIMBERLY CHONG
PATENT EXAMINER

Attachment(s)

15☐ Notice of References Cited, PTO-892

16☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

17☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 13 & 14

18☐ [illegible]

19☐ [illegible]

20☐ [illegible]

DETAILED ACTION

This Office action is in response to the communication filed July 27, 2001, Paper No. 16.

Claims 1, 3-8, 10-15, 17-19, 21 and 22 are pending in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 1, 3-8, 10-15, 17-19, 21 and 22 are rejected under 35 U.S.C. 112, first paragraph, for the reasons of record set forth in the Office action mailed April 24, 2000 and January 18, 2001, Paper Nos. 5 and 12 respectively. Applicants' arguments have been considered but they are not persuasive. Applicants argue that the scopeof the claims, which scope is drawn to compositions and methods for reversing drug resistance or inducing apoptosis in a cell in vitro or in vivo comprising the administration of an antisense molecule which targets nucleic acids encoding glucosylceramide synthase, or, in combination, the administration of a chemosensitizing or chemotherapeutic agent. Such scope, which includes the successful administration, targeting and functional expression of antisense in appropriate target cells in an organism whereby a reversal or drug resistance and target cell apoptosis is obtained, is highly unpredictable data must be provided for such treatment effects upon administration of antisense The data provided in the

instant disclosure provide enablement for the targeting and delivery of antisense which inhibit the expression of the target nucleic acid encoding glucosylceramide synthase in vitro, and for the subsequent in vitro induction of apoptosis in such target cells. The instant disclosure provides data enabling for the reversal of drug resistance in a cancer cell in vitro comprising the administration of antisense which target and inhibit the expression of nucleic acids encoding glucosylceramide synthase.

Applicants assert that specific examples exist in the art and have been provided in the instant specication which teach vectors into which the antisense of glucosylceramide synthase may be inserted for in vivo applications, and teach methods and formulations for enhancing antisense stability and the like (i.e. relevant methods and formulations for in vivo applications). Contrary to Applicants' assertions, such citations and reiterations of vectors, methods and formulations which exist in the prior art do not address the unpredictability of the instant antisense in providing in vivo effects. Such data must be provided enablement for the scope claimed. The data provided which illustrates in vivo effects following combination therapy is not equivalent to the ability of glucosylceramide synthase antisense to provide such effects in the absence of (combined administration of) the chemotherapeutic agent and the antisense.

Applicants assert that the formulations claimed have utility other than in vivo application. The utility of such formulations is not in dispute. The claims which comprise fomulations read on in vitro and in vivo applications (i.e. "... for reversing drug resistance in a cancer cell or inducing

apoptosis in a cancer cell...") and hence are rejected for lacking enablement for the scope claimed, which scope includes in vivo treatment effects provided in an organism.

New Rejections

Claim Rejections - 35 USC § 103

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-8, 10-15, 17-19, 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ichikawa et al in view of Milner et al, the combination in view of Liu et al and Lucci et al insofar as the claims are drawn to the compositions and methods for reversing drug resistance and inducing apoptosis in a target cell in vitro comprising the administration of an antisense oligonucleotide which targets and inhibits the expression of a nucleic acid encoding glucosylceramide synthase and optionally additionally administering a chemosensitizer or chemotherpeutic agent to the target cell in vitro.

Ichikawa et al teach (The Ichikawa reference as cited in the Office action mailed April 24, 2000, Paper No. 5) nucleic acids encoding glucosylceramide synthase as well as teaching the functional expression of human glucosylceramide synthase (See especially figure 6, page 4642).

Ichikawa et al do not teach the generation of antisense targeted to human glucosylceramide synthase.

Milner et al teach (the Milner reference as cited in the Office action mailed April 24, 2000 , Paper No. 5) methods of designing and testing antisense oligonucleotides in their ability to target and inhibit the expression of a target gene of known nucleotide sequence in vitro, including antisense which target the sense strand encoding full length glucosylceramide synthase, as well as antisense oligonucleotides comprising lengths between 15 and 25 nucleotides (See entire document).

Liu et al(Reference C1 of the IDS provided by Applicants as Paper No. 14, filed June 25, 2001) teach the expression of glucosylceramide synthase and the resulting increase in drug resistance of target cells transfected with recombinant glucosylceramide synthase in vitro (See especially the abstract and figure 3 on page 1144).

Lucci et al (Reference C2 of the IDS provided by Applicants as Paper No. 10, filed January 12, 2001) teach the correlation between increases in glucosylceramide levels and the induction of apoptosis in drug resistant target cells in vitro following their treatment with agents which inhibit the conversion of ceramide to glucosylceramide in combination with the

administration of the chemotherapeutic agent doxorubicin to such target cells (See entire document, especially the abstract; figure 2 on page 303 and the text on pages 305-306).

It would have been obvious to one of ordinary skill in the art to engineer antisense oligonucleotides which target nucleic acids encoding glucosylceramide synthase since the nucleic acid sequence encoding glucylceramide synthase had been disclosed by Ichikawa et al and the protocol for designing and testing the ability of antisense oligonucleotides to effectively target and inhibit the expression in vitro of a nucleic acid target with known sequence had been taught previously by Milner et al. One of ordinary skill in the art would have been motivated to generate antisense to inhibit glucosylceramide synthase, since the correlation between increased glucosylceramide synthesis and increases in cellular drug resistance had been taught previously by Liu et al, whereby the transfection of recombinant glucosylceramide synthase into target cells conferred drug resistance onto those cells in vitro. One of ordinary skill in the art would have expected that the inhibition of expression of glucosylceramide synthase by antisense would decrease or inhibit the formation of glucosylceramide in those target cells and would subsequently decrease drug resistance in such target cells. One of ordinary skill in the art would also have expected that the inhibition of glucosylceramide synthesis, combined with the administration of a chemotherapeutic agent to target cells in vitro would elicit apoptosis in those target cells because the eliciting of apoptosis in target cells following the administration of inhibitors of glucosylceramide synthesis in combination with the administration of doxorubicin had resulted in eliciting apoptosis in target cells in vitro, as taught previously by Lucci et al. Therefore, one of

ordinary skill in the art would have expected that the targeting and inhibition of expression of glucosylceramide synthase by antisense in drug resistant target cells in vitro, combined with administration of a chemosensitizing agent would confer drug susceptibility and elicit apoptosis in such target cells in vitro.

Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a

general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SEAN McGARRY
PRIMARY EXAMINER

JZ

October 9, 2001